PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/053321	07.12.2004	12.12.2003

International Patent Classification (IPC) or both national classification and IPC
C12Q1/48, G01N33/50

Applicant
SIRENADE PHARMACEUTICALS AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/053321

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 22-27

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☒ the claims, or said claims Nos. 23-27 are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 22-27 (partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,6-7,10,13,15-17,19-21
	No:	Claims	1,3-5,8-9,11-12,14,18,22-27
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-27
Industrial applicability (IA)	Yes:	Claims	1-27
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The subject-matter of claims 22-27 relate to a compound and its medical uses, defined by reference to a desirable characteristic or property, namely identified by the method of claims 1 to 21. However no technical features characterizing the said compound (e.g. structure), which would permit the skilled person to unambiguously identify it, are given in claims 22-27 which therefore lacks clarity (Art. 6 PCT). Thus, a search over the whole of the claimed scope was impossible. Only those compounds clearly and unambiguously defined in the description by technical features have been searched, i.e. compounds PP1-Chr, PP2, SU6656 (p.42, l.6-7 of the description and fig.9(p)) and geldanamycin, 17-AAG, radicicol (p.44, l.13-14 of the description).
An opinion with regard to novelty, inventive step and industrial applicability is thus given only in relation to those part of the above mentioned claims which have been searched, namely those parts relating to the above mentioned compounds.

2. The subject-matter of claims 23 to 27, directed to first and second medical uses of the above mentioned compounds and to pharmaceutical composition containing the said compounds does not meet the requirements of Art. 5 and 6 EPC.
The description gives merely proof-of-principle experiments in order to validate the screening method of claim 1. The said compounds have only been used as experimental tools. However, no data and/or evidence that the said compounds can be used as a medicament for the treatment of diseases which are caused by Src family kinase is given. Compounds being suitable for medical uses need, for instance, to fulfil some requirements like low toxicity. Furthermore, document D4 concluded that the property of PP1 and its related compounds appear to limit their usefulness as pharmacological agents in the treatment of T cell-mediated disease, their discovery represents a significant advance in the use of tyrosine kinase inhibitors as tools to study the role of Lck and FynT in T cell signalling. Document D5 teaches that geldanamycin "proved to be too hepatotoxic for clinical use" (p.S57, left-hand column, first two lines).

   Thus, in the absence of any further technical details and/or evidence to demonstrate

that the said compounds have some therapeutical effects, serious doubt exist as to whether all of the claimed compounds can be used as medicaments.
Thus, the broad scope of claims 23 to 27 is not supported by the description (Art. 5 PCT) which would give sufficient guidance to the skilled man to carry out the invention over the whole claimed range (Art. 6 PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The following documents D are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

   D1: US-A1-2003162222
   D2: WO-A-0042042
   D3: Chemistry And Biology (London) (03-2000), 7(3), 225-235
   D4: Journal Of Biological Chemistry, American Society Of Biological Chemists, Baltimore, Md, Us (12-01-1996), 271(2), 695-701
   D5: Trends in Molecular Medicine (2002), 8(4)(Suppl.), S55-S61
   D6: Expert Opinion On Investigational Drugs, Ashley Publications Ltd., London, Gb (07-2001), 10(7), 1327-1344
   D7: Trends In Pharmacological Sciences, Elsevier Trends Journal, Cambridge, Gb (01-12-2000), 21(12), 489-495

2. The subject-matter of claim 1 is not new (Art. 33(2) PCT).
   Document D1 discloses a method for identifying inhibitors of Src kinase Hck wherein the WT kinase and mutated kinase (threonine 338 of the ATP binding site is mutated to various residues) are expressed in Cos7 cells, the said cells are then contacted with PP1 and a change in the phenotype of the cells is determined (see p.5, paragraph (0080)).
   D2 discloses the same method of identifying inhibitors of the v-Src kinase wherein WT and I338G v-Src (a mutation in the ATP binding site which does not alter the biological function of the kinase) are expressed in NIH3T3 cells (see p.83, l. 23 to p. 89, l. 2).

D3 discloses a similar method wherein a compound (AP22161) is tested for its ability to revert the morphology and inhibit the growth of rat fibroblasts transformed with mutant cSrcY527F which is a constitutively active kinase (the mutation has been carried out at the regulatory tyrosine residue (phosphorylation site))(p.228, section "Effect of compounds.....transformed cells" to end of this section on p. 229).

3. For the same reasons, the subject-matter of dependent claims 3-5 (see D3 above), 8-9 (see D1 and D2 above), 11, 12 (D1 is concerned with the Hck kinase wherein the threonine of the ATP binding site is mutated, see above point 1), 14 and 18 are also not new (Art. 33(2) PCT)

4. The subject-matter of claims 2, 6-7, 10, 13, 15-17, 19-21 appears to be new (Art. 33(2) PCT) but does not involve an inventive step in the sense of Art. 33(3) PCT as the features of claims 15, 17, 19 and the inducible expression system of claims 2, 16, 20-21 are routine in the art.
Moreover, documents D1 to D3 already disclose the concept of determining the specificity of an inhibitor using a cell-based assay system by comparing the phenotype of the cells expressing the WT with cells expressing the mutant in presence and absence of the inhibitor. Thus it would appear that the embodiment of claims 6-7 is a mere obvious variation of the said concept wherein a known "kinase dead" mutant is involved.
Similarly, claims 10 and 13 are other embodiments wherein, respectively, two mutations are combined on the same mutant or wherein different cells express different mutants. The said embodiments do not lead to any unexpected effect and therefore do not meet the requirements of Art. 56 EPC.

5. The subject-matter of claim 22 (with the restriction mentioned under point 1 of Item III) is not new (Art. 33(2) PCT). It is clear from the description (p. 42, l. 6-7 and p. 44, l. 13-14) and from D1, D4 to D7 (passages as cited in the ISR) that the compounds mentioned under point 1 of Item III are commercially available and/or well known in the art.

6. Notwithstanding the objections raised under Articles 5 and 6 PCT in point 2 of Item III, it would appear that the subject-mater of claims 23 to 27 is formally not new (Art.

33(2) PCT) as document D5 discloses that the inhibitor 17-AAG is in phase I clinical trial as chemotherapeutic agent (abstract).

Re Item VII
Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 to D6 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII
Certain observations on the international application

1. The subject-matter of claims 6 and 7 is not clear as the said claims are directed to the use of a "kinase dead" form of a Src kinase in a method of identifying a compound which modulates the activity of a Src kinase by determining a change in the phenotype of the cells. It would however appear that the said mutant does not lead to any particular phenotype and thus it is not clear how the said mutant can be used to identify a compound which modulates the activity of the said mutant by determining a changing in the phenotype of the cells (Art. 6 PCT).